## REMARKS

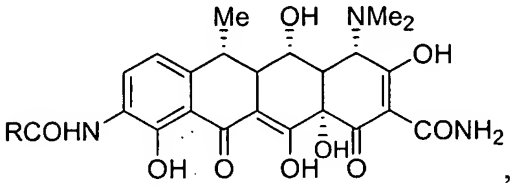
Claims 1-76 and 82 were pending in the application. Claims 1, 19, 21, 23, 25, 28, 53, 55, 76 and 82 have been amended, and claims 20 and 22 have been cancelled without prejudice. Therefore, claims 1-19, 21, 23-76 and 82 will be pending upon entry of the present amendment.

No new matter has been added. Support for the amendments to claim 1 can be found, for example, at least in original claim 22 and at page 6, lines 13-14, and at page 6, lines 23-24 of the specification as originally filed. Support for the amendments to claim 19 can be found, for example, at least in original claim 22 and at page 6, lines 23-24 of the specification as originally filed. Claims 21 has been amended to provide proper dependency. Claims 23 and 25 have been amended to provide proper dependencies and support for the further amendments to claims 23 and 25 can be found, for example, at least in original claim 22 and at page 6, lines 23-24 of the specification as originally filed. Support for the amendments to claim 28 can be found, for example, at least at page 23, line 36 of the specification as originally filed. Claim 53 has been amended to correct minor informalities, such as punctuation errors and support for the further amendments to claim 53 can be found, for example, at least at page 10, lines 9-10, and at page 24, line 10 through page 25, line 2 of the specification as originally filed. Claim 55 has been amended to correct minor informalities, such as punctuation errors, and support for the further amendments to claim 55 can be found, for example, at least at page 10, lines 9-10, and at page 24, line 10 through page 25, line 2 of the specification as originally filed. Support for the amendments to claim 76 can be found, for example, at least at page 24, line 10, through page 25, line 2 of the specification as originally filed. Support for the amendments to claim 82 can be found, for example, at least in original claim 22 and at page 6, lines 13-14, and at page 6, lines 23-24 of the specification as originally filed.

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

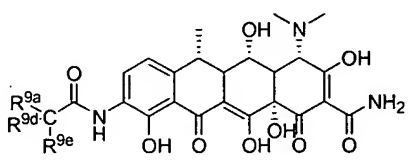
***Rejection of Claims 1-5, 11-13, 16, 18-20, 22 and 82 under 35 U.S.C. §102(b)***

Claims 1-5, 11-13, 16, 18-20, 22 and 82 are rejected under 35 U.S.C. §102(b) as being anticipated by Barden *et al.*, "Glycylcyclines 3. (Aminodoxycyclinecarboxamides." *J. Med. Chem.* 37(2); 3205-3211 (1994). Specifically, the Examiner indicates that Barden *et al.* disclose compounds and pharmaceutical compositions of the formula:

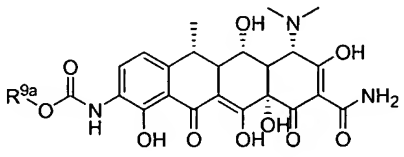


, in which R is $Me_2CH$, MeO, $(CH_2)_4NCH_2$, $(CH_2)_5NCH_2$, $Me_2NCH_2$, $Et_2NCH_2$, $t$-$C_4H_9NHCH_2$ and $n$-$C_4H_9NHCH_2$.

Applicants respectively traverse. Barden *et al.* teach compounds as exemplified in structures **A** and **B**:



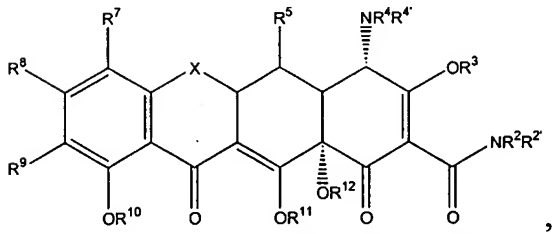
A



B

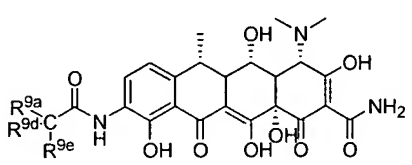
in which $R^{9a}$ is hydrogen or methyl; and $R^{9d}$ and $R^{9e}$ are each independently hydrogen, methyl, dialkylamino or alkylamino.

As amended, claims 1 and 82 are directed to compounds of formula I:

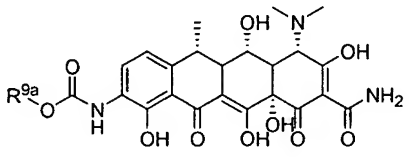


, in which X is $C^{6'}C^{6}$; $R^2$, $R^{2'}$, $R^3$, $R^6$, $R^7$, $R^8$, $R^{9c}$, $R^{10}$, $R^{11}$ and $R^{12}$ are hydrogen, $R^4$, $R^{4'}$ and $R^{6'}$ are alkyl; $R^5$ is hydroxyl, $R^9$ is $NR^{9c}C(=Z')ZR^{9a}$, Z is $CR^{9d}R^{9e}$, $NR^{9b}$ or oxygen; Z' is oxygen; $R^{9a}$ $R^{9d}$, and $R^{9e}$ are each independently ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or $R^{9d}$ and $R^{9e}$ may be linked to form a ring; and $R^{9b}$ and $R^{9c}$ are each independently hydrogen, alkyl,

alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic or heteroaromatic. More specifically, as amended, claims 1 and 82 are directed to compounds as exemplified in structures **A** and **B**:



A

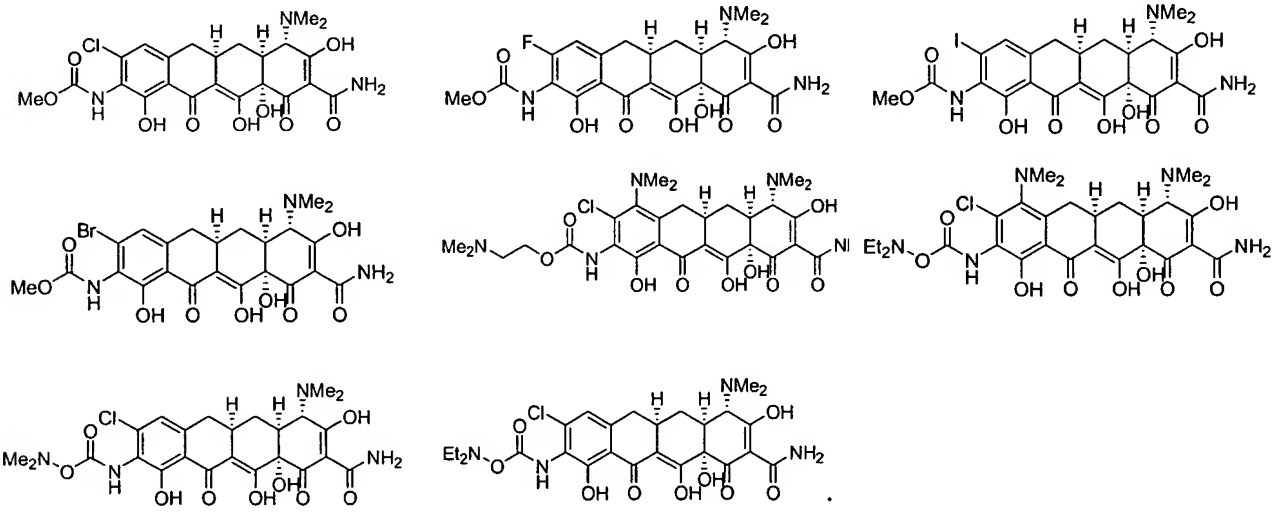


B

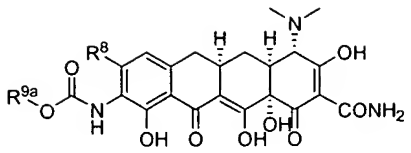
in which $R^{9a}$, $R^{9d}$ and $R^{9e}$ each independently ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic, absent, or $R^{9d}$ and $R^{9e}$ may be linked to form a ring. Barden *et al.* do not teach or suggest compounds such compounds, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §102 (b).

***Rejection of Claims 1, 11-13, 16, 19, 20-22 and 82 under 35 U.S.C. §102(b)***

Claims 1, 11-13, 16, 19, 20-22 and 82 are rejected under 35 U.S.C. §102(b) as being anticipated by Sum *et al.* (U.S. Patent No. 5,430,162). Specifically, the Examiner indicates that Sum *et al.* disclose compounds of the formula:



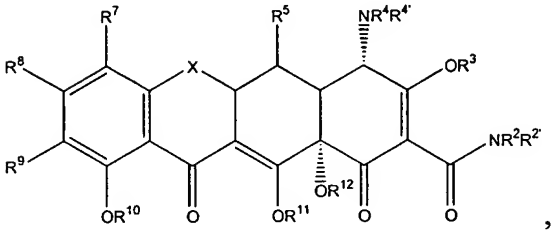
Applicants respectfully traverse. Sum *et al.* teach compound as exemplified in structure **C**:



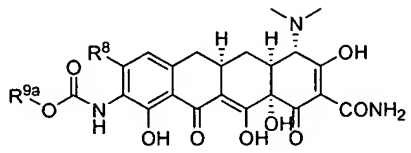
C

in which $R^8$ is chlorine, bromine, fluorine or iodine.

As amended, claims 1 and 82 are directed to compounds of formula I:



, in which X is $C^{6'}C^6$; $R^{6'}$, $R^2$, $R^{2'}$, $R^3$, $R^6$, $R^7$, $R^{9c}$, $R^{10}$, $R^{11}$ and $R^{12}$ are hydrogen, $R^4$, $R^{4'}$ and are alkyl; $R^5$ is hydroxyl, $R^9$ is $NR^{9c}C(=Z')ZR^{9a}$, Z is oxygen; Z' is oxygen; $R^8$ is hydrogen and $R^{9a}$ is ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic or heteroaromatic. More specifically, amended claims 1 and 82 are directed to compounds as exemplified by compound **C**:

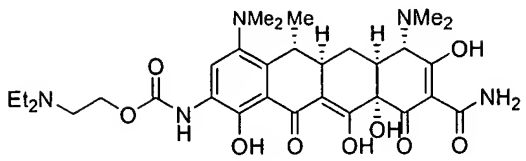
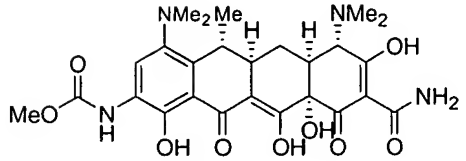
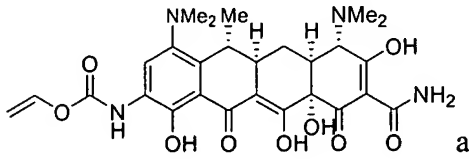
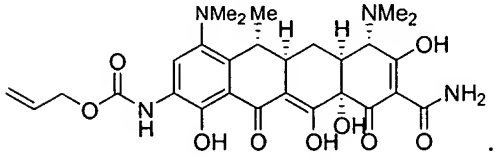


C

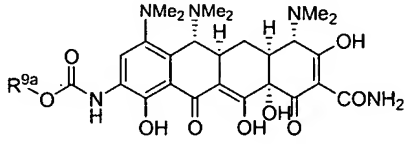
in which $R^8$ is hydrogen. Sum *et al.* do not teach or suggest compounds such compounds and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §102 (b).

***Rejection of Claims 1-6, 11-13, 16, 20-22 and 82 under 35 U.S.C. §102(b)***

Claims 1-6, 11-13, 16, 20-22 and 82 are rejected under 35 U.S.C. §102(b) as being anticipated by Hlavka *et al.* (U.S. Patent No. 5,494,903). Specifically, the Examiner indicates that Hlavka *et al.* disclose compounds and pharmaceutical compositions of the formula:




and


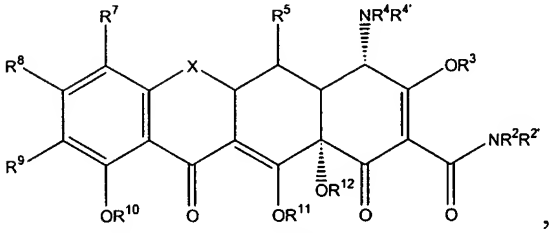
Applicants respectfully traverse. Hlavka *et al.* teach compounds exemplified by structure **D**:



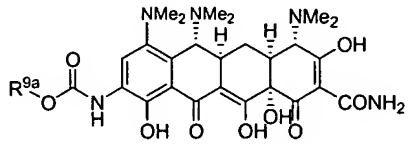
**D**

in which $R^{9a}$ is dialkylaminoalkyl, alkyl, alkyenyl and allyl.

As amended, claims 1 and 82 are directed to compounds of formula I:



, in which X is $C^{6'}C^{6}$; $R^2$, $R^{2'}$, $R^3$, $R^6$, $R^7$, $R^{9c}$, $R^{10}$, $R^{11}$ and $R^{12}$ are hydrogen, $R^4$, $R^{4'}$ and $R^{6'}$ are alkyl; $R^9$ is $NR^{9c}C(=Z')ZR^{9a}$, Z is oxygen; Z' is oxygen; $R^{9a}$ is ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic or heteroaromatic. More specifically, amended claims 1 and 82 are directed to compounds exemplified by structure **D**:



**D**

in which $R^{9a}$ is ethyl, t-butyl, n-butyl, i-butyl, or n-pentyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, arylsulfonyl, alkoxycarbonyl, arylcarbonyl, alkylamino, arylalkyl, aryl, heterocyclic or heteroaromatic. Hlavka *et al.* do not teach or suggest such compounds, and therefore, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §102 (b).

***Rejection of Claims 1-10, 41-55, 69-76 and 82 under the Doctrine of Obviousness-type Double Patenting***

Claims 1-10, 41-55, 69-76 and 82 are rejected under the judicially created doctrine of obviousness as being unpatentable over claims 1-26, 32 and 51-81 of U.S. Patent No. 6,818,634. Specifically, the Examiner states that "[t]he products claimed in the instant application are disclosed in the prior art" and that "[o]ne of ordinary skill in the art would be motivated to produce the compounds of the instant application with the disclosure of the '634 patent."

While in no way admitting that Claims 1-10, 41-55, 69-76 and 82 are obvious over claims 1-26, 32 and 51-81 of U.S. Patent No. 6,818,634, upon allowance of the present application, Applicants will consider submitting a terminal disclaimer in compliance with 37 C.F.R. 1.321(b) and (c), if appropriate, which will obviate the rejection.

***Rejection of Claims 1, 5, 9, 19, 27, 28, 63 and 82 under 35 U.S.C. §112, second paragraph***

Claims 1, 5, 9, 19, 27, 28, 63 and 82 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

At section (1), the Examiner indicates that claims 1, 9, and 82 are indefinite for reciting the phrase "prodrug moiety."

Applicants respectfully submit that a skilled artisan in possession of the specification would have been able to reasonably understand the term "prodrug moiety" at the time the invention was made. The term "prodrug" is defined at least at page 24, lines 10-17, of the specification as originally filed as "compounds which are converted *in vivo* to active forms..." The specification further defines the term "prodrug moiety," at least at page 24, line 17 through page 25, line 2. Specifically, the specification states that

> [t]he language "prodrug moiety" includes moieties which can be metabolized *in vivo* to yield an active compound. For example, the term includes moieties which can modify certain functional groups of the substituted tetracycline

> compounds...Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (*e.g.*, propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (*e.g.*, dimethylaminoethyl ester), acylamino lower alkyl esters (*e.g.*, acetyloxymethyl ester), acyloxy lower alkyl esters (*e.g.*, pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (*e.g.*, benzyl ester), substituted (*e.g.*, with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides.

The specification further states, at page 6, lines 11-13, that

> [e]xamples of prodrug moieties include, for example, acyl esters and propionoic acid esters. In certain embodiments, the prodrug moiety is aroyl, alkanoyl, or alkaroyl and may or may not be cleaved *in vivo* to the hydroxyl group.

One of skill in the art would have been able to use the specification to determine the appropriate prodrug moiety to be used in the preparation of the prodrugs of the tetracycline compounds of the invention. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection to claims 1, 9 and 82.

At section (2), the Examiner indicates that claim 5 is indefinite for the recitation of the term "derivative." Specifically, the Examiner states that "[a] derivative is copied or obtained from something else."

Applicants respectfully traverse. The specification as originally filed states, at page 5, lines 29-33, that

> [t]he term "tetracycline compound" includes many compounds with a similar ring structure to tetracycline. Examples of tetracycline compounds include: tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, doxycycline, and minocycline. Other derivatives and analogues comprising a similar four ring structure are also included. Table 1 depicts tetracycline and several known tetracycline derivatives.

One of ordinary skill in the art with access to the specification at the time the invention was made would have been able to determine that the term "derivative" meant tetracycline compounds based on the structures of tetracycline, chlortetracycline, oxytetracycline, demeclocycline, methacycline, sancycline, doxycycline, and minocycline. Further, Table 1 at page 6 of the specification as originally filed provides the structures of the above-mentioned tetracycline derivatives. Thus, a skilled artisan would have been able to use Table 1 at page 6 as well as the

description to determine appropriate tetracycline derivatives. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

At section (3), the Examiner indicates that claims 19 and 27 are indefinite for the recitation of the term "multicyclic." Specifically, the Examiner asserts that the definition defines "multicycle," but not multicyclic."

Applicants respectfully submit that a skilled artisan in possession of the specification would have been able to reasonably understand that the term "multicyclic" denotes being related to a multicycle, which is defined in the specification at page 23, lines 24-26, as referring "to two or more cyclic rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, *e.g.*, the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings." One of ordinary skill in the art and in possession of the specification at the time of the invention would reasonably be able to determine the meaning of the term "multicyclic." Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

At section (4), the Examiner indicates that claim 28 is indefinite for the recitation of the term "steroidyl."

Applicants respectfully traverse. As amended, claim 28 is directed to a tetracycline compound of the invention in which $R^{9a}$ is a steroid. Applicants submit that the term "steroid" was well known in the art at the time the invention was made and is defined at page 23, line 36, as a multicyclic group such as cholesterol. A skilled artisan at the time the invention was made and in possession of the specification would have been able to determine suitable steroids for use in the invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 28.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 5, 9, 19, 27, 28, 63 and 82 under 35 U.S.C. §112, second paragraph.

***Claim Objections***

Claims 53 and 55 have been amended, as suggested by the Examiner, to incorporate the word "and" before the last compound in each list of compounds. Therefore this objection to the claims is moot.

Claim 55 has been further amended as suggested by the Examiner, to insert a period. Therefore this objection to the claims is moot.

Claims 14-18, 20-26, 29-40, 56-62 and 64-69 are objected to as being dependent upon a rejected base claim. Applicants respectfully submit that the amendments to the claims renders this objection moot.

## SUMMARY

In view of the above amendment, applicant believes the pending application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: May 4, 2006

Respectfully submitted,

By _____

Cynthia M. Soroos
Registration No.: 53,623
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant